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Retroviruses and Schizophrenia Revisited

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Both genetic and environmental factors appear to contribute to the causation of schizophrenia. Evidence indicating that fetal development is disrupted in schizophrenia and the finding of an excess of winter births among schizophrenic patients have led to continued speculation that an intrauterine viral infection may cause developmental lesions, genetic mutations, or persistent infections that lead to schizophrenia. Certain unique characteristics of the retroviruses render them plausible as candidate "schizoviruses" and the involvement of an endogenous retrovirus would be compatible with some of the puzzling epidemiological findings in schizophrenia. Reverse transcriptase (RT) is a retrovirally encoded enzyme essential for retroviral integration into host DNA. While attempts to detect retroviral infections by measuring RT activity in the peripheral lymphocytes and serum of schizophrenic patients have been unsuccessful, such negative findings may simply mean that the virus is not active in peripheral lymphocytes. A more sensitive and comprehensive approach to detect a retrovirus is to search the genomes of schizophrenic patients directly for the presence of retroviral DNA sequences encoding RT and one possible approach is described.

KEY WORDS: schizophrenia, etiology, neurodevelopment, virus, retrovirus

INTRODUCTION

Despite intensive research, the cause of schizophrenia remains unknown. Probably the best established finding is that genetic factors make a significant contribution to the etiology of the disorder [Kendler and Diehl, 1993]. However, the considerable deviation from 100% concordance rates for schizophrenia among monozygotic twins implies that in addition to genes some environmental factor(s) is involved. Viral infection is one environmental agent which has been proposed as contributing to the causation of schizophrenia [Torrey, 1988]. The consideration of a viral etiology stems in part from the observation of psychotic symptoms in association with various viral encephalopathies [Wilson, 1976; Halstead et al., 1988; Perry, 1990] and also from the reported seasonality of birth of persons who subsequently develop schizophrenia [Bradbury and Miller, 1985]. To date, however, attempts to detect evidence of increased rates of viral infection in schizophrenic patients or indeed to identify a specific virus associated with the illness have failed [Kirch, 1993].

The lack of success of these studies does not, however, exclude a role for a virus. Indeed evidence of viral infection may be impossible to obtain if the infection took place many years before the onset of schizophrenia. Furthermore, only a limited number of viruses have been assessed for a possible etiological role in schizophrenia, i.e., we may simply have examined the wrong virus.

EARLY NEURAL DEVELOPMENT

The risk of schizophrenia in non-identical twins of schizophrenic probands is about 17% compared to 9% in non-twin siblings [Gottesman, 1991] despite the fact that members of a pair of fraternal twins and a pair of full siblings share the same average degree of genetic relationship, i.e., 50%. Although there is some recent conflicting evidence [Klaning et al., 1994], most studies report that schizophrenia is no more common in twins than in singletons [Luxenburger, 1928; Rosenthal, 1960; Allen and Pollin, 1970; Kendler and Robinette, 1983]. If this is the case, then the increased risk for fraternal twins cannot be the result of complications of twinning per se but would appear to be the consequence of sharing the intrauterine environment contemporaneously with a schizophrenic proband. This suggests that some aspect of the prenatal environment plays a significant role in the risk of developing schizophrenia.

Indeed, substantial evidence has accumulated which indicates that a sizable subgroup of schizophrenic patients have experienced a disruption of intrauterine de-

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velopment. Thus, a number of authors have reported high rates of minor physical abnormalities among schizophrenic patients [Gualtieri et al., 1982; Guy et al., 1983; Green et al., 1989, 1994; Lane et al., 1993]. These abnormalities are thought to arise during the first trimester of pregnancy. Moreover, there is evidence of dermatoglyphic abnormalities in schizophrenic patients [Mellor, 1968, 1992; Bracha et al., 1991]. The dermal ridges develop between the third and fifth month of gestation [Penrose and Ohara, 1973] and remain unchanged thereafter. Thus dermatoglyphic abnormalities represent a "fossilised" record of developmental perturbation occurring between the latter part of the first and the middle of the second trimester of pregnancy. Finally, there are reports of neuronal disarray in the hippocampi of a significant portion of schizophrenics [Scheibel and Kovelman, 1981]. This alteration in neuronal architecture is thought to result from impaired neuroblast migration into the primitive hippocampus: a migration which reaches its peak in the early to mid-portion of the second trimester [Scheibel and Conrad, 1993].

Recent research has also indicated that individuals who develop schizophrenia demonstrate high rates of neuromotor [Fish et al., 1992; Walker et al., 1994] and sensorimotor abnormalities [Fish et al., 1992] during their infancy again pointing to an early disruption of neurodevelopment.

Although a genetic factor could conceivably predispose to dysmorphogenesis, the variation of the physical abnormalities between individual cases and the diversity of the neurological findings in these reports suggest that these aberrations are not the consequence of a single gene defect but more likely result from an environmental insult during the second trimester that affects the development of both ectodermal and neurodermal tissue.

VIRUSES AND SCHIZOPHRENIA

While viral infection constitutes only one of many potential types of fetal insult, it is notable that a number of viruses such as rubella virus and cytomegalovirus cross the placenta to produce fetal abnormalities ranging from gross defects such as microcephaly to subtle dysmorphology in the distal upper limb [Achs et al., 1966; Purvis-Smith and Menser, 1973] which is similar to that observed in schizophrenic patients. Furthermore, epidemiological support for the assertion that development may be disrupted by a virus is provided by the consistent reports that an excess of individuals who develop schizophrenia are born in the winter months [Bradbury and Miller, 1985]. The seasonal variation in the births of schizophrenics parallels the seasonality of many viral infections [Torrey et al., 1977].

If viruses do play a role in the pathogenesis of schizophrenia a logical first step is to ask, "based on existing knowledge of viral diversity, which virus (or viral groups) is the most likely candidate agent?" To date most attention has focused on the herpesviruses, which may have a number of characteristics that make them plausible candidate viruses in schizophrenia, e.g., they are widely distributed, known to be neurotropic, and demonstrate persistence and/or latency of effect. However, attempts to find evidence of previous infection with members of this group of viruses have failed [Kirch, 1993]. Detection of viruses, however, typically depends on either the presence of an active infection permitting direct assay of virions, viral genomes, viral gene products, or antibodies against viral proteins. If viral infection during fetal life predisposes to the development of schizophrenia beginning some 20 years later, it may be impossible with most candidate viruses to directly demonstrate a correlation between infection and schizophrenia. Thus it is perhaps not surprising that to date no consistent association has been found between schizophrenia and infection by herpesviruses or any other group of viruses [Kirch, 1993].

Influenza virus also merits consideration in view of the recent epidemiological data suggesting an association between maternal influenza infections in the second trimester of pregnancy and subsequent development of schizophrenia in the offspring [O'Callaghan et al., 1991]. However, a number of studies have failed to find an association even when the same influenza epidemics were studied [Crow et al., 1991]. Thus the role of influenza viruses in schizophrenia remains contentious.

A third family of viruses, the retroviruses, are attractive candidate agents in schizophrenia because of their distinctive life-cycle and pathogenic potential. Retroviruses contain two identical copies of single-stranded ribonucleic acid (RNA). An essential characteristic of these viruses is that they possess a unique enzyme called reverse transcriptase that functions as a deoxyribonucleic acid (DNA) polymerase. It catalyses the transcription of the viral RNA genome into DNA. The double stranded DNA is then able to integrate into the host cell DNA by recombination to form a "provirus." The viral genes remain integrated for the lifetime of the host cell and are replicated along with chromosomal DNA during subsequent mitotic or meiotic cell division. If the retrovirus integration site is in the coding or regulatory portion of a gene, the insertion event can have significant phenotypic effects: thus retroviral infections are considered mutagenic. Retroviruses can remain latent in their proviral form for years before becoming reactivated at which time various cellular pathologies may develop and infectious virions may be produced and dispersed to infect other cells.

RETROVIRUSES AND DISEASE

At present, four retroviruses are known to affect humans: the human T-cell leukaemia viruses HTLV-I and HTLV-II, and the human immunodeficiency viruses HIV-1 and HIV-2. A fifth species, human spumaretrovirus, has been isolated from human brain tissue but is not known to be associated with disease.

If retroviral infection of the germ line occurs (either through direct infection of sperm or ova cells or following infection of the fetus prior to the differentiation of the germline cells) the provirus may become a permanent part of the species gene pool. Such "endogenous" retroviruses are transmitted across generations as stable chromosomal elements, yet may retain the ability to

replicate and produce infectious virions. Infectious endogenous retroviruses have not as yet been identified in humans although they are known in several animal species [Coffin, 1982]. On the other hand, sequences from replication-defective human endogenous retroviruses have been identified [Bonner et al., 1982; Leib-Mosch et al., 1990; Larsson et al., 1989; Kreig et al., 1992] and some of these are transcriptionally active [Larsson et al., 1989].

Although no example has yet been found where an endogenous retrovirus causes human disease, the similarity of their actions to those of the other transposable elements (such as the *Alu* and LINE1 sequences) suggest that they may be important pathogens. There are four disorders, neurofibromatosis type 1 [Wallace et al., 1990], haemophilia A [Dombroski et al., 1991], haemophilia B [Vidaud et al., 1993], and Huntington's disease [Goldberg et al., 1993] where causal mutations induced by the insertion of *Alu*, or LINE1 sequences have been reported. The *Alu* and LINE1 families of repeat sequences are members of a broader class of nonviral "retroid elements" that like retroviruses transpose via an RNA intermediate with the help of the enzyme reverse transcriptase.

An expectation of any virus involved in the causation of schizophrenia is that it would be neurotropic and indeed retroviruses show a propensity for neurotropism in both humans and animals. Thus two of the four retroviruses known to affect humans cause neurological disease. HIV-I causes an encephalopathy which can present with a variety of psychiatric symptoms [Halstead et al., 1988; Perry, 1990]. HTLV-I, the cause of some cases of acute T-cell leukaemia, is believed to be the cause of tropical spastic paraplegia, a neurological disorder which affects the dorsal columns of the spinal cord [McFarlin, 1991]. A number of the lentivirus subfamily of retroviruses cause encephalitis in their animal hosts, simian immunodeficiency virus in macaque monkeys [Letvin et al., 1985], visna virus in sheep [Hasse, 1986; Narayan and Cork, 1985], caprine arthritis encephalitis virus in goats [Narayan and Cork, 1985], and equine infectious anaemia virus in horses [McClure et al., 1982].

PATHOGENESIS

The retrovirus hypothesis of schizophrenia as first envisioned by Crow was a restricted one, wherein he suggested that a retrovirus integrates near a gene that normally controls the early development of cerebral dominance [Crow, 1984]. Using the analogy of the known ability of certain human retroviruses to produce tumours by integration near and regulatory disruption of cellular proto-oncogenes, he suggested that the hypothetical schizophrenia virus might contribute to a specific disruption of brain development that later manifests as schizophrenia. Crow's original hypothesis demands that the putative retrovirus integrates at one of a small number of specific sites within the human genome. It is now clear, however, that there are a number of mechanisms by which retroviruses could produce their pathological effects.

1) Retroviral infection may produce pathophysiological change through direct cellular damage. As has been suggested for other viruses such as the influenza virus [Scheible and Conrad, 1993] this may occur during a critical phase of gestation and lead to a neurodevelopmental defect which is later expressed as schizophrenia. Such teratogenic effects of infection are well recognised.

2) A retroviral infection during the intrauterine development could result in integration of the retrovirus at random (and possibly multiple) sites within the genome of brain cells. Subsequent periodic reactivation and viral dissemination to other neurones could then produce the picture of relapse and remission which characterises the course of schizophrenia. Such transpositions commonly occur in nature.

3) A retrovirus may incorporate a gene which is capable of inducing a psychosis. If such a "schizovirus" integrates in a human host it could produce psychotic symptoms in a manner analogous to the viral oncogenes.

These three mechanisms do not require that the virus integrate at a specific site. Although it was initially thought that retroviruses integrated randomly in the host genome it is now clear that selective "hotspots" for integration occur [Sandmeyer et al., 1990; Craigie, 1992].

4) The integration site may of course be site specific and disrupt the functioning of critical brain genes. We would conjecture that the normal expression of the putative gene(s) is age and development dependent implying that the disruption of this gene becomes critical only when the normal gene function is needed during adolescence or adult life. In this model the pathogenesis of schizophrenia is the result of mutation in normal human genes caused by the integration/transposition of the viral sequence. Such a model is compatible with transpositions by either exogenous and or endogenous sequences. As stated above mutational events in a number of genetic diseases are now known to involve such a mechanism.

EPIDEMIOLOGY OF SCHIZOPHRENIA

If the integration of an endogenous retrovirus is causally related to the development of schizophrenia it could explain two of the enigmas of the epidemiology of the disorder, i.e., the continued presence of the illness at high prevalence despite the fact that it confers a markedly reduced fertility [Odegaard, 1972] and the observation that children of schizophrenic probands have a higher lifetime risk of developing the disorder than do the parents of probands.

The lifetime risk of developing schizophrenia is between 0.5 and 1% [Torrey, 1987] much higher than that of any known single gene disorder. A retrovirus can easily account for the persistence of the disorder despite natural selection. Thus the majority of patients may inherit the causative endogenous retrovirus from a parent, while a minority acquire the virus through intrauterine infection. Where germline cells are involved in this latter group of patients the integrated retrovirus

would subsequently follow vertical transmission. Such a paradigm would have the effect of adding genetically vulnerable cases to the population and counterbalancing the negative impact of the reduced fertility. We note that alternative explanations for the persistence of the illness at high prevalence have been proposed, e.g., that schizophrenic phenotype may confer some, as yet, unrecognised survival advantage, or that polygenic inheritance may shield, from natural selection, genes which predispose individuals to develop schizophrenia [Gottesman et al., 1982].

The morbid risk for schizophrenia is almost twice as high in children as opposed to parents of schizophrenics, i.e., 13% and 6%, respectively [Gottesman, 1991]. This difference in morbidity risk is usually attributed to the decreased fertility associated with schizophrenia, a factor which reduces the morbid risk for a parent but not a child of a schizophrenic. We note, however, that the morbid risk for uncles and aunts of schizophrenic probands is also half the risk of their nieces or nephews (2% and 4%, respectively, despite the fact that a proband shares the same genetic relationship with both sets of relatives) [Gottesman, 1991], a finding which is more difficult to explain on the basis of reduced fertility. This pattern of differential morbid risk between generations is compatible with a model where a portion of cases of schizophrenia are caused by an endogenous retrovirus. Thus as outlined above retroviral infection with germline integration would result in two etiologically distinct types of schizophrenia, some patients inheriting the retrovirus from a parent and others acquiring it during intrauterine infection. The parents of the former but not of the latter probands would be at increased risk for schizophrenia. By contrast children from both groups would be at increased risk.

It seems unlikely that any of the four known human exogenous retroviruses are involved in the causation of schizophrenia as these viruses are prevalent in specific human populations defined by geography or specific behaviour patterns [Curran, 1992]. This assumption is supported by the observations of Robert-Guroff who reported that only two of thirty schizophrenic patients studied had serum antibodies for human retroviruses (i.e., one was positive for HTLV-I, another for HTLV-II, and none for HIV-II) [Robert-Guroff et al., 1985]. Thus if an exogenous retrovirus causes schizophrenia we must propose that it is an as yet unidentified species.

A role for an endogenous retrovirus would satisfy one of the major criticisms of viral theories of the causation of schizophrenia, i.e., the seeming incompatibility between the relatively uniform prevalence rates for schizophrenia throughout the world [Sartorius et al., 1986] and the typical geographic variation in rates of most viral infections. Endogenous retroviral sequences on the other hand appear to be ubiquitous in human DNA. Crow has postulated that one of these endogenous retroviruses transposes from a dormant area of the human genome to a critical site in the male germ cell line and that this transposition may be temperature dependent [Crow, 1987] thus accounting for the recognised season of birth effect.

Endogenous retroviruses may replicate and integrate at different sites within the germ cells. Such retroviral insertions provide an alternative mechanism (other than expanding trinucleotide repeats) to explain the phenomenon of anticipation which has been observed in some families of schizophrenics [Bassett and Horner, 1994; Wetterberg and Farmer, 1991; Bleuler, 1978; Slater and Cowie, 1971]. However, at present the role and biological significance of endogenous retroviruses remains poorly understood.

THE SEARCH FOR EVIDENCE OF RETROVIRAL INVOLVEMENT IN SCHIZOPHRENIA

The search for retroviruses in schizophrenia and other diseases has relied on the detection of the enzyme reverse transcriptase (RT) or its gene RT *pol*. As RT is an obligate enzyme of retroviruses, activity of RT is a footprint which indicates the presence of a retrovirus. The search for traces of RT activity in schizophrenic patients has been unsuccessful to date. Thus RT activity was not detected in the lymphocytes of schizophrenic patients [Feenstra et al., 1988, 1989; Coggiano et al., 1991] nor were anti-RT antibodies found in the serum of hospitalized schizophrenic patients [DeLisi and Sarin, 1985]. There are two limitations of the above studies which make false-negative findings likely. First, these experiments were performed using blood and consequently would not have detected a retrovirus that was harboured exclusively in brain cells. We note, however, that to date all infective retroviruses known to affect humans are all T-cell lymphotropic [Sarngadharan et al., 1986]. A more important shortcoming is that RT is synthesised only as the virus is about to integrate in the host genome. Therefore RT activity would not be detected if retrovirus integration took place many years before the onset of illness. Thus failure to detect RT activity in lymphocytes and anti-RT antibodies in serum of schizophrenic patients does not exclude a role for retroviruses in the causation of the disorder.

FUTURE RESEARCH

A more direct experimental approach and one which is more likely to be conclusive in either establishing or ruling out a retroviral cause of schizophrenia (including the possible involvement of an endogenous retrovirus) is to search the genome of schizophrenic patients and control subjects for schizophrenia associated sequences of retroviral origin.

The problem is how to screen the human genome efficiently for the presence of both known and unknown animal and human endogenous retroviruses. Fortunately the obligate retroviral gene *pol* encoding the enzyme RT exhibits a high degree of sequence conservation in all known retroviruses. One should be able to use this property in a search of retroviral species specific to schizophrenia. Oligonucleotide primers could be synthesized to be used in PCR protocols to enable the amplification of all retroviral related-sequences from the genomic DNA from schizophrenic patients and appropriately matched controls. The amplification prod-

uct could then be characterized for sequence specificity in the two groups of genomic DNA with a view to the identification of schizophrenic specific retroviruses using a number of novel molecular techniques including "representational difference analysis" [Lisitsyn et al., 1993]. Representational difference analysis is a variation of subtractive hybridisation techniques which enable the investigator to characterise the differences between two complex genomes. This methodology is particularly suited for characterization of PCR products and has been successfully used to isolate probes to viral genomes present as single copies in human DNA [Lisitsyn et al., 1993]. Thus this approach would represent a significant advance on our ability to rule in or rule out involvement of this intriguing group of viruses in the etiology of schizophrenia.

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